REMARKS

No claims are amended herein. The Office states that previously-added claims 19 and 21-32 are drawn to non-elected species, as Applicants previously elected *Streptococcus* group B (Action at page 2). Without acquiescence, the current claim listing uses status identifies indicating same. Accordingly, claims 11-13 and 16-32 are pending, with claims 11-13, 16-18, and 20 currently under active examination.

Withdrawal of Rejections

Applicants note with thanks the withdrawal of all previous rejections (Action at page 2), leaving the only outstanding rejection as an obviousness rejection.

Rejection under 35 U.S.C. §103(a)

Claims 11-13, 16-18, and 20 are rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over Michon et al. US 6,602,508 ("Michon") in view of Chatfield WO 99/15671 ("Chatfield") (Action at pages 2-4). Specifically, the Office contends that Michon teaches multivalent Group B *Steptococcus* ("GBS") conjugate vaccines, comprising different types of GBS capsular polysaccharides conjugated to a protein, such as tetanus toxin (Action at pages 3-4). While acknowledging that Michon fails to teach Fragment C, the Office points to Chatfield to overcome this deficiency (Action at page 3). According to the Office, Chatfield teaches a polypeptide comprising tetanus toxin Fragment C, or a fragment thereof, in a conjugate vaccine that "does not increase a patient's anti-tetanus titer response" and that may include other antigens to provide a multivalent conjugate vaccine (Action at page 4). The Office concludes that one of skill in the art would have been motivated by Chatfield's teachings of multivalent conjugate

vaccines to conjugate Fragment C to Michon's GBS capsular polysaccharide, thus rendering it *prima facie* obvious to combine Michon's and Chatfield's teachings and arrive at the claimed invention. *Id.*

Applicants respectfully traverse, because Chatfield in fact fails to teach a conjugate vaccine that "does not increase a patient's anti-tetanus titer response", as required by the claims, and further teaches away from the use of other than peptide antigens, such as the use of polysaccharide antigens. Moreover, any *prima facie* case of obviousness is overcome by the surprising and unexpected results achieved with the claimed invention.

1) Neither Michon nor Chatfield teach or suggest a conjugate vaccine that "does not increase a patient's anti-tetanus titer response"

It is axiomatic that to establish *pima facie* obviousness of a claimed invention, all claim limitations must be taught or suggested by the prior art. See, e.g., *In re Royka*, 490 F.2d 981, 985 (CCPA 1974) (holding that obviousness requires a suggestion of all limitations in a claim). Neither Michon nor Chatfield, however, teach or suggest the unexpected result that a conjugate vaccine, which uses tetanus toxin Fragment C as the carrier, in fact does not increase a patient's anti-tetanus titer response.

Claim 11, the only independent claim currently under examination, recites that the conjugate vaccine "does not increase a patient's anti-tetanus titer response." The Office contends that Chatfield's conjugate vaccine also "does not increase a patient's anti-tetanus titer response," pointing for support to the reference's Abstract, claims, and Figures (Action at page 4). Nonetheless, Applicants are at a loss to identify any such a teaching in Chatfield's Abstract or claims or Figures. Chatfield is directed to tetanus toxin Fragment C, or a fragment thereof, fused to the pre-S1 and/or pre-S2 region of hepatitis B virus, or a fragment thereof, and vaccines comprising same. The Abstract describes as much, as do the claims, which further recite a

polynucleotide encoding the fusion polypeptides, and vectors of host cells comprising same, as well as methods of using such compositions. Nowhere is there any mention of the anti-tetanus titer response.

Chatfield's Figures similarly are devoid of any teaching of this element. Figure 2 illustrates total immunoglobulin response for anti-Fragment C, 14 days post prime dose and 7 days post boost dose, with each of two conjugates of Fragment C fused to pre-S1/pre-S2 regions, and is the only Figure directed to the anti-tetanus response. Analysis of Figure 2, however, shows increased anti-Fragment C response to both conjugates at both times, compared with the normal mouse sera control (see Figures 4A and 4B). That is, the graphs of Figures 4A and 4B show the normal mouse sera response to anti-Fragment C well below that of mice inoculated with either Fragment C conjugate vaccine, except at very high dilutions.

Accordingly, in contrast to the Office's contentions, and as noted in our previous response, Chatfield fails to teach or suggest this element of the claims. Moreover, Michon cannot remedy this deficiency, because Michon, as acknowledged by the Office, fails even to mention Fragment C. As neither cited reference teaches or suggests an element of the claims, Applicants respectfully submit, there can be no *prima facie* case of obviousness.

2) Chatfield in fact teaches away from the use of other than peptide antigens

As noted above, Chatfield is directed to tetanus toxin Fragment C, or a fragment thereof, fused to a pre-S1 and/or pre-S2 region of hepatitis B virus, or a fragment thereof. These regions of hepatitis B virus are all peptide regions. Chatfield notably never mentions or even hints at conjugating Fragment C to any other type of antigen, such as the polysaccharide antigen of the subject claims. Thus Chatfield teaches exclusively peptide antigen-Fragment C conjugates, rather than polysaccharide antigen-Fragment C conjugates.

Furthermore, Chatfield discloses producing the conjugate vaccine product as a fusion polypeptide, where nucleic acid sequences encoding the hepatitis B virus peptide antigen and Fragment C are operably linked, allowing the fusion product to be expressed therefrom (see, e.g., Chatfield, page 6, line 28 to page 7, line 8). Since such an approach is inapplicable to making the claimed polysaccharide antigen-Fragment C conjugates, we respectfully submit that the reference in fact teaches away from the use of such antigens.

Furthermore, Chatfield discusses DNA vaccines, where the vaccine product comprising a nucleic acid sequence encoding the peptide antigen and Fragment C is administered directly as a naked nucleic acid construct (see, e.g., Chatfield, page 8. lines 17-21). Again, as such a vaccination approach is inapplicable to vaccines comprising polysaccharide antigens, as here, the reference leads a person of skill in the art away from the subject matter of the instant claims, and indeed away from any type of antigen other than peptide antigens.

Accordingly, as a "teach away" reference, Chatfield cannot properly be combined with Michon to arrive allegedly at the invention of the claims, preventing any *prima facie* case of obviousness. ("It is improper to combine references where the references teach away from their combination." *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983); MPEP 2145 X (D)(2)).

3) Unexpected Results of the Claimed invention further destroy any* prima facie *case of obviousness

Applicants respectfully submit that the unexpected results obtained with the claimed invention further destroy any *prima fac*ie case of obviousness based on combining the Michon and Chatfield references. ("A proper rejection based on the rationale that the claimed invention is a combination or prior art elements also includes a finding that results flowing from the combination would have been predictable to a person of ordinary skill in the art." Examination Guidelines Update: Developments in the Obviousness Inquiry After *KSR v. Teleflex*, 75 FR

53643, 53647 (September 1, 2010) ("2010 KSR Guidelines Update"), referencing MPEP 2143 A(3); see also *Crocs, Inc. v. U.S. International Trade Commission*, 598 F.3d 1294, 1310 (Fed. Cir. 2010) (reversing a finding of obviousness based on the combination of two references, one teaching a clog and the other teaching a heel strap, where the combination yielded "more than predictable results."). That is, even if there is a *prima facie* case, it is abrogated by evidence herein of unexpected results flowing from the claimed invention. See *Takeda Chemical Indus. v. Alphapharm*, 492 F.3d 1350 (Fed. Cir. 2007) (affirming the district court's findings regarding no *prima facie* obviousness where, even if a *prima facie* case had been established, it would have been overcome in view of the unexpected results); 2010 KSR Guidelines Update, at p. 53652.

Applicants have surprisingly discovered that using Fragment C, rather than the entire tetanus toxin, as a carrier protein for polysaccharide antigens, rather than peptide antigens, unexpectedly results in reduced or no increase in anti-tetanus titer response, while producing similar or enhanced response to the polysaccharide antigen. As discussed in the specification, the use of tetanus toxin as a carrier in conjugate vaccines has lead to a rising concern that the vaccinated population will be over-exposed to tetanus, with the concomitant risk of inducing tolerance and/or hypersensitivity (see, e.g., paragraph [0006] of the published application, US 2007/0014812). In addressing this concern, the instant specification discloses *for the first time* that Fragment C of tetanus toxin can be used as a carrier protein for polysaccharide antigens to provide conjugate vaccines, which surprisingly do not induce the otherwise-expected tetanus toxin antibodies in animals immunized therewith (see, e.g., paragraph [0019]; emphasis added).

Figure 5 and Table 4 of the instant specification provide experimental evidence of these surprising results, with respect to conjugate vaccines of Fragment C with GBS polysaccharides (see, e.g., Example 2). Specifically, Figure 5 indicates that GBS polysaccharide conjugates with

Fragment C elicit similar or significantly higher polysaccharide-specific IgG titers than the corresponding conjugate vaccines comprising the whole tetanus toxin (see, e.g., paragraphs [0053] to [0054]). Moreover, Table 4 indicates that the anti-tetanus IgG response in mice immunized with the Fragment C conjugates is dramatically reduced when compared to the response using the corresponding tetanus toxin conjugates (see, e.g., paragraphs [0055] to [0057]). Similar results are seen with other polysaccharide antigen-Fragment C conjugates, both in terms of exhibiting similar or improved response to the polysaccharide antigen and in terms of exhibiting no or reduced anti-tetanus response (see, e.g., paragraphs [0046] to [0052], Figures 3 and 4, and Table 3).

Applicants respectfully submit that the reduced anti-tetanus response with similar or better antigenic immunogenicity, as disclosed in the instant application, could not have been predicted by one of skill in the art in view of the cited references. Accordingly, the fact that the claimed conjugate vaccine "does not increase a patient's anti-tetanus titer response", as required by the claims, destroys any *prima facie* case of obviousness. Compare *In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007) (finding that a claimed anti-venom composition of antibody fragments, rather than whole antibodies or whole antibodies combined with the fragments, which exhibited the unexpected property of neutralizing the lethality of rattlesnake venom while reducing the occurrence of adverse immune reactions, was a relevant unexpected property); 2010 KSR Guidelines Update, at pp. 53657-58; see also *Sanofi-Synthelabo v. Apotex. Inc.*, 550 F.3d 1075 (Fed. Cir. 2008) (finding a claimed isolated enantiomer not obvious where the enantiomer exhibited unexpectedly strong therapeutic advantages over the prior art racemic mixture, without the corresponding expected toxicity); 2010 KSR Guidelines Update, at p. 53655.

For at least one or more of the above reasons, Applicants respectfully request withdrawal of the 103(a) rejections directed at the subject claims.

While Applicants have distinguished the subject claims from the art of record based on recited elements of independent claim 11, the only independent claim currently under examination, Applicants reserve the right to separately address the patentability of the dependent claims in the future, should that become necessary.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. 50-3732, Order No. 00518-105055.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 50-3732, Order No. 00518-105055.

Respectfully submitted,
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Dated: February 7, 2011

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